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Cardiac Surgery

Improving the Quality of Coronary Bypass Surgery With Intraoperative Angiography

Validation of a New Technique

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OBJECTIVES We report a comprehensive assessment and validation of a new intraoperative angiography technique.

BACKGROUND Technical problems at the site of the distal anastomosis compromise an underappreciated proportion of coronary bypass grafts. The absence of a systematic, validated technique to verify graft patency in the operating room represents a significant breach in quality assurance.

METHODS Fluorescent indocyanine green (ICG) dye is excited with dispersed laser light to create an angiographic depiction of the graft, native vessel, and anastomosis. One-hundred twenty patients underwent ICG angiography. Angiograms were reviewed for reliability and validity studies.

RESULTS A total of 348 coronary bypass grafts were studied. Each ICG angiogram took 2.2 ± 1.1 min to perform. The ICG angiography found 4.2% of patients had significant graft problems requiring major revision. Quality of visualization was rated according to a seven-point Likert scale (1 = worst, 7 = best). Among conduits, saphenous veins were best visualized (mean score ± standard deviation), 6.4 ± 1.5 versus 5.5 ± 1.9 for internal mammary arteries and 4.4 ± 2.3 for radial arteries ($p = 0.02$). Location of distal anastomosis did not influence quality of visualization. There was high inter-rater reliability for graft revision (kappa = 1.0) and graft patency (kappa = 0.97) between surgeons. Sensitivity and specificity of the ICG angiograms for graft stenosis >50% was 100% among 22 grafts also studied with X-ray angiography.

CONCLUSIONS Information from ICG angiograms led to graft revisions for technical problems in 4.2% of patients that would have otherwise gone unrecognized. Intraoperative angiography is an emerging tool for improving the quality of coronary bypass surgery. (J Am Coll Cardiol 2005;46:1521–5) © 2005 by the American College of Cardiology Foundation

Graft patency is the major determinant of survival and freedom from repeat intervention after coronary bypass surgery. The construction of a technically perfect anastomosis at the time of surgery is an important determinant of graft patency. Modern coronary bypass series report perioperative graft occlusion rates as high as 11% (1,2). Technical errors in bypass graft construction by the operating surgeon are primarily responsible for these early failures. There is currently no standardized approach for identifying these errors using any form of intraoperative graft assessment, and it is not routine clinical practice in most centers. We present reliability studies and validation of a simple technique of intraoperative fluorescent dye angiography that provides high-fidelity angiographic images similar to those of catheter-based X-ray angiography.

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MATERIALS AND METHODS

This study was a prospective evaluation of the reliability and validity of a new diagnostic imaging modality: indocyanine green (ICG) dye fluorescence angiography.

Contrast agent. Indocyanine green is a negatively charged, polymethine tricarbocyanine dye (chemical formula $C_{43}H_{47}N_2NaO_6S_2$) with absorbance and fluorescence maxima in the near infrared (750 to 1,000 nanometer = 1 billionth of a meter) region, where very few molecules show intrinsic fluorescence and there is little background fluorescence. When illuminated at 806 nm, ICG fluoresces to emit light centered at 830 nm. Indocyanine green is non-covalently (95%) bound to albumin and is not nephrotoxic. It is taken up from the plasma by hepatic parenchymal cells and secreted into the bile.

Imaging device. The imaging device (Novadaq Technologies Inc., Concord, Ontario, Canada) is composed of an imaging head containing an 806-nm laser light source and a charge-coupled device video camera equipped with an optical filter to block transmission of visible and 806-nm light while optimizing transmission of ICG-

Abbreviations and Acronyms

ICG = indocyanine green
TIMI = Thrombolysis In Myocardial Infarction

fluoresced light at 830 nm. Eye protection is not required in the operating room because the laser light energy (2.0 W) is dispersed. The imaging head is positioned over the exposed heart, and the laser is activated before the first pass of a bolus of ICG through the field of view. Images of the coronary arteries and bypass grafts are acquired at a rate of 30 frames/s and may be viewed in real time. The near-infrared light can maximally penetrate 1 to 2 mm of soft tissue. The fluorescence sequentially shows illumination of the graft or coronary artery lumen, a blush of the epicardium as dye passes through the microcirculation, and finally, washout through the coronary veins. Optimal methods of dye injection for each type of graft in on-pump and off-pump coronary surgery were developed and are presented in Table 1.

Patients. All patients signed a consent form approved by the local institutional review ethics board after being approached by a study coordinator who was not affiliated with their clinical care. Operations were performed by six experienced surgeons who each perform at least 200 cardiac operations per year. Exclusion criteria included allergy to ICG dye and cardiogenic shock.

Patients underwent coronary bypass surgery according to the standard technique, and ICG angiography was performed on all bypass grafts. Grafts deemed to be occluded by ICG angiography in the operating room underwent revision, and operative findings were noted. Images were assessed off-line for determination of surgeon-specified image quality and inter-rater agreement. A small subgroup of six patients with 22 grafts underwent subsequent catheter-based X-ray angiography a pilot study for a randomized clinical trial. The X-ray angiograms were read by a cardiologist blinded to the results of the intraoperative studies.

Statistical methods. Categorical variables are presented as proportions and percentages, and continuous variables are presented as mean values with standard deviations. Comparison of means for surgeon assessment of quality of visualization were performed using one-way analysis of variance. Inter-rater agreement for graft revision, patency, and Thrombolysis In Myocardial Infarction (TIMI) flow grade (3) was determined using the Cohen kappa statistic. Sensitivity and specificity were calculated according to standard methods.

Table 2. Pre-operative Patient Characteristics (n = 120)

Characteristic	Mean ± SD or n (%)
Age (yrs)	67.6 ± 9.1
Gender	
Male	94 (78.3%)
Female	26 (22.1%)
Diabetes	32 (26.7%)
Hypertension	80 (66.7%)
Dyslipidemia	76 (63.3%)
Urgent surgery	64 (53.3%)
Repeat operation	2 (1.7%)
Smoker	69 (57.5%)
Peripheral vascular disease	13 (10.8%)
NYHA functional class III or IV	91 (75.8%)
Ejection fraction <30%	17 (14.2%)
Preoperative MI	56 (46.7%)

MI = Myocardial infarction; NYHA = New York Heart Association.

RESULTS

Between September 2002 and January 2004, 120 patients were recruited. Comprehensive graft assessment was performed in all patients. Patient characteristics are reported in Table 2. Patients were generally representative of the overall coronary bypass population at our institution. Operative characteristics are presented in Table 3. In total, 348 grafts were performed, with a mean of 2.9 grafts per patient. The vast majority of bypasses were performed on-pump, as is our routine clinical practice. A total of 432 ICG angiograms were performed, with a mean of 3.6 ± 0.9 ICG angiograms performed per patient. Typically, we performed one angiogram for each distal anastomosis and one angiogram for all proximal anastomoses. Average time to perform one ICG angiogram was 2.2 ± 1.1 min/patient. A representative angiogram of left internal mammary artery bypass graft is presented in Figure 1.

Using ICG angiography, we found that 4.2% (5 of 120) of patients had significant graft problems requiring major anastomotic revision or new graft construction. These graft

Table 1. Optimal Dye Injection Methods for Indocyanine Green Angiography

Anastomosis and Graft to Be Assessed	Dye Delivery Method	ICG Dye Dosage (mg)
Distal anastomosis		
In-situ grafts on-pump: LIMA, RIMA, GEA	Injection into aortic cannula	2.5
In-situ grafts off-pump: LIMA, RIMA, GEA	Injection into central venous line	1.25
Free grafts: SVG, radial, free IMA	Direct graft injection before proximal anastomosis construction	0.0125
Proximal anastomosis, free grafts SVG, radial, free IMA	Injection into central venous line after weaning from cardiopulmonary bypass	1.25

GEA = gastroepiploic artery; ICG = indocyanine green; IMA = internal mammary artery; LIMA = left internal mammary artery; Off-pump = performed without cardiopulmonary bypass on a beating heart; On-pump = performed with cardiopulmonary bypass on an arrested heart; RIMA = right internal mammary artery; SVG = saphenous vein graft.

Table 3. Operative Data

Characteristic	Mean ± SD or n (%)
Total number of bypassed vessels	348
Mean number of bypassed vessels	2.9 ± 0.8
Off-pump	4 (3.3%)
Mean cross-clamp time, min	82 ± 32
Mean cardiopulmonary bypass time, min	112 ± 31
Number of ICG angiograms	432
Mean number of ICG angiograms	3.6 ± 0.9
Mean time per ICG angiogram, min	2.2 ± 1.1
Conduits revised/conduits studied	
LIMA	1/119 (0.9%)
RIMA	0/8 (0%)
Radial artery	0/67 (0%)
Saphenous vein grafts	4/154 (2.6%)
Patients requiring major graft revision	5/120 (4.2%)

Abbreviations as in Table 1.

problems included twisted vein graft (1), significant lesion in native vessel distal to the graft-coronary artery anastomosis (2), and technical problems at the anastomosis (2). A representative angiogram is shown in Figure 2. A further four grafts (3.3%) required minor revision based on intraoperative findings. These included graft repositioning (1) and extra sutures to improve hemostasis (2).

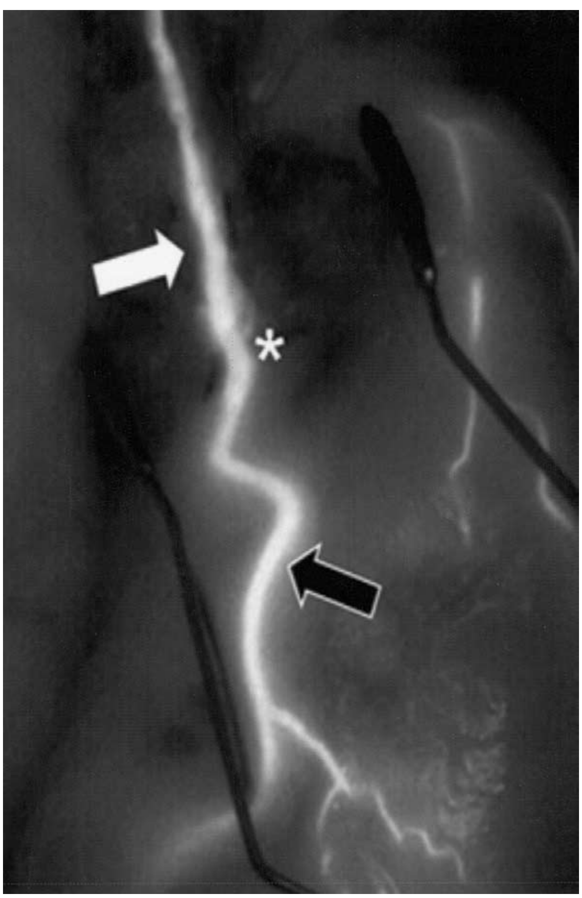

Figure 1. Indocyanine green angiograms of an in-situ left internal mammary artery **(white arrow)** bypass to left anterior descending coronary artery **(black arrow)**. The distal anastomosis is well seen and denoted by the **asterisk**.

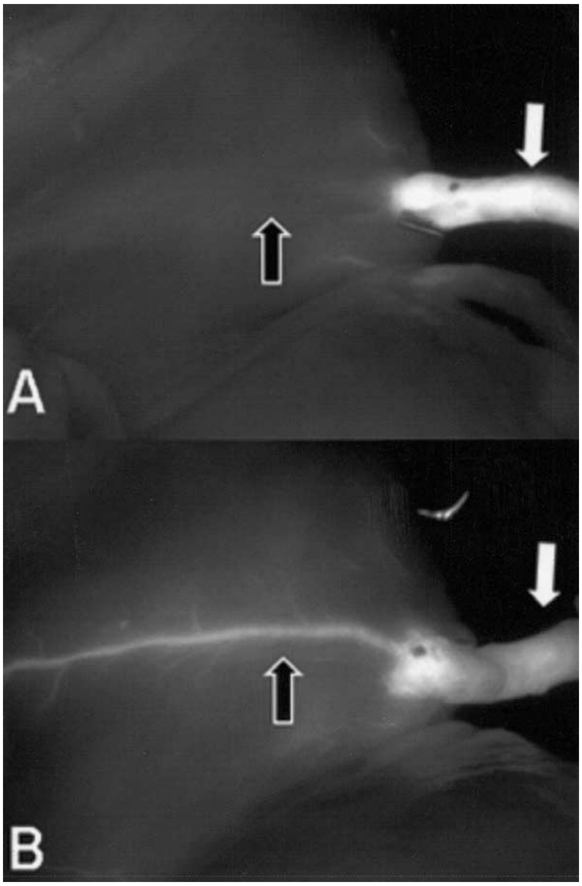

Figure 2. Indocyanine green angiogram of a saphenous vein graft. **(A)** There is contrast dye in the vein graft **(white arrow)**, but no dye enters the distal posterior descending coronary artery **(black arrow)**. The distal anastomosis was reopened, and an occlusive stitch was found penetrating through the posterior wall of the target coronary vessel preventing antegrade flow. The anastomosis was revised. In the post-revision angiogram **(B)**, contrast was observed to rapidly fill the vein graft **(white arrow)** and distal coronary vessel **(black arrow)**.

Angiographic results are summarized in Table 4. Quality of visualization was rated according to a seven-point Likert scale (1 = worst, 7 = best). Among conduits, saphenous veins were best visualized (mean score ± standard deviation) 6.4 ± 1.5 versus 5.5 ± 1.9 for internal mammary arteries and 4.4 ± 2.3 for radial arteries, analysis of variance overall $p = 0.02$. Location of distal anastomosis did not influence quality of visualization.

Inter-rater agreement among two surgeons, one experienced and one inexperienced with the technique, was 100% (Cohen kappa = 1.0) for assessing total graft occlusion and 97% (Cohen kappa = 0.9) for assessing graft revision when 35 ICG angiograms were reviewed off-line. Inter-rater agreement for assessing TIMI flow grade was only 60% (Cohen kappa = 0.4).

As part of a pilot investigation for a randomized clinical trial, six patients, with a total of 22 bypass grafts, underwent gold-standard post-operative X-ray angiography for comparison with ICG angiogram images. Perianastomotic lesions with >50% stenosis or graft occlusion were observed in three grafts (i.e., there were three true positives). The

Table 4. Validity and Reliability Studies of Indocyanine Green Angiography

Visualization by Graft Type and Distal Territory	Quality of Visualization (1 = Worst, 7 = Best)	p Value
Graft type		
Internal mammary	5.5 ± 1.9	
Saphenous vein	6.4 ± 1.5	0.02*
Radial artery	4.4 ± 2.3	
Distal territory		
Inferior wall	5.1 ± 2.3	
Lateral wall	5.1 ± 2.1	0.52*
Anterior wall	5.7 ± 1.9	
Inter-rater reliability	**Percent Agreement**	**Kappa**
Graft revision†	100%	1.0
Graft patency‡	97%	0.9
TIMI flow grade	60%	0.4
Validity Versus X-Ray Angiography	**Sensitivity Test Positive/ True Positive (%)**	**Specificity Test Negative/ True Negative (%)**
>50% stenosis or occlusion	3/3 (100%)	19/19 (100%)

*One-way analysis of variance for overall comparison between the three groups. †Surgeon stated he/she would revise graft based on ICG angiogram findings. ‡Surgeon believed graft was 100% patent based on ICG angiogram.
ICG = indocyanine green; TIMI = Thrombolysis In Myocardial Infarction.

sensitivity of ICG angiography to detect occlusion or >50% stenosis was 100% (3 positive ICG studies/3 true positives). There were no false positives, and specificity for ICG angiography for occlusion or >50% stenosis was also 100% (19 negative ICG studies/19 true negatives). Representative angiograms are shown in Figure 3.

DISCUSSION

With the exception of coronary artery bypass surgery, virtually all other interventions on the heart, including cardiac valve repair and coronary stenting, are accompanied by completion diagnostic imaging to ensure an adequate technical result. Despite tremendous improvements in the quality of processes of care in cardiac surgery over the past decade, there is still no well-accepted or broadly used technique to assess the quality of the bypass graft itself. Recent angiographic trials by Puskas et al. (4) and Khan et al. (5) have shown significant clustering of the technical results of off-pump surgery at the level of the individual surgeon, highlighting the need for intraoperative quality assurance.

In this study, we determined that in a high-volume academic practice, nearly 1% of internal mammary artery grafts and 3% of saphenous vein grafts required graft

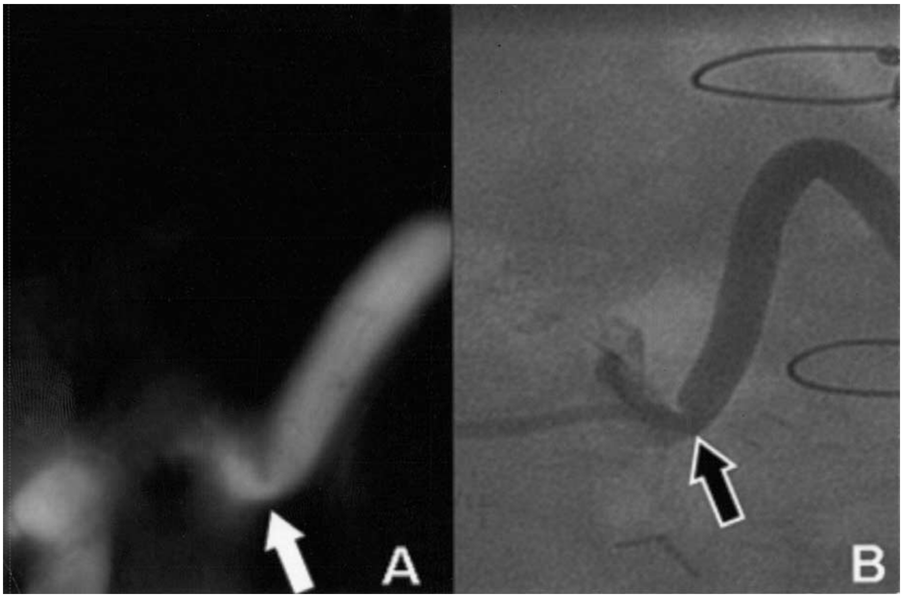

Figure 3. Comparison angiographic images of a kinked proximal vein bypass graft-aorta anastomosis seen on intraoperative indocyanine green angiogram **(A, white arrow)**. The graft was repositioned without revision of the anastomosis. A post-operative conventional X-ray angiogram shows a similar lesion despite repositioning **(B, black arrow)**.

revision when completion ICG angiography was performed for intraoperative quality assessment. When analyzed by patient, 4.2% of patients required graft revision. These results are similar to those of other groups who have used this technology (6,7). In all cases, the lesions would have otherwise been missed by the operating room team. The clinical consequences of early graft failure are not benign. A recent report suggests that the perioperative mortality in patients with unrecognized graft problems is over 9% (8).

Among graft assessment techniques currently available, contrast dye X-ray coronary angiography is the gold standard. Difficulties incorporating bulky equipment into the cardiac operating room and safety concerns regarding nephrotoxicity and embolic/bleeding complications have limited implementation of intraoperative X-ray angiography. Graft assessment techniques such as thermal angiography, Doppler flow measurement, and electromagnetic flow measurement have also been attempted in the operating room with limited success (9–12). More recently, transit-time ultrasound flow measurement has gained significant implementation, particularly in off-pump coronary surgery. Despite the ease of use of this technique, several investigators have raised concerns regarding the diagnostic accuracy of transit-time flow measurements, particularly in non-occlusive stenoses (13).

After promising pre-clinical investigations with this technique, we performed the first human studies in 2002 (14). Subsequently, we have embarked on a rigorous systematic approach to intraoperative graft patency assessment using ICG angiography. The technique showed perfect inter-rater reliability for graft patency among two surgeons, one with significant experience in the technique and one with no previous experience with the technique, suggesting that interpretation of images does not require significant training or a learning curve. There was poor inter-rater reliability for graft TIMI flow grade. Because most free grafts in the series were hand injected, the subjective interpretation of TIMI flow grade was dependent on the rate of injection by the surgeon or assistant, which were not standardized. Pedicled grafts were less well seen with ICG angiography, likely because of fat and muscular tissue overlying the artery, which scatters the fluorescence signal. To improve pedicled graft visualization, our current practice is to partially skeletonize the distal portion of the graft from its overlying muscle and fat. For an average coronary bypass case, the total extra time needed to perform intraoperative patency assessment will be 8 to 10 min, including 6 or more minutes while the aortic cross-clamp is applied.

As part of a pilot study for a clinical trial, 22 grafts were also imaged with X-ray angiography. Included in his cohort were three grafts that intraoperatively were believed to have non-occlusive but >50% stenoses that were not corrected because of concerns regarding prolonging operative time. In these three grafts, gold-standard X-ray angiography confirmed that there was a true hemodynamically significant lesion.

Because ICG angiography may be able to identify most graft lesions before chest closure, its potential effect on early graft patency may be greater than perioperative aspirin use, anti-lipid medications, and arterial grafting. Currently, drug-eluting stent therapies for coronary disease provide low single-digit early failure rates, and without high quality intraoperative patency assessment, it is unlikely that the periprocedural failure rates of coronary bypass grafts can remain competitive.

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